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EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,366	FRONDOZA ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-38 and 54-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-38 and 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Claims 1-35, 39-53 and 58-70 are cancelled. Claims 36-38 and 54-57 are pending. The Terminal Disclaimer filed 1/24/07 is acknowledged and is acceptable. As mentioned in the previous office action, the priority date for the instant application is 08/06/01.

2. Applicant's arguments filed 01/24/07 have been fully considered but they are not fully persuasive. The Double Patenting rejection is withdrawn in light of the Terminal Disclaimer filed by applicant 1/24/07. The 112 2nd rejection over claim 38 is withdrawn in light of applicant's amendment dated 1/24/07.

3. However, the 112 2nd rejection over claim 54 is maintained. In applicant's remarks dated 1/24/07, applicant states that the term "substantially" was removed from claim 54 for all phrases including from "substantially shorter that the first time period" and "substantially solid form" and "substantially fluid state" (see page 4-5 of applicant's remarks). However, applicant amended claim 54 to remove the term "substantially" only in the one phrase "substantially shorter that the first time period". Thus the phrases "substantially solid form" and "substantially fluid state" remain in claim 54, and thus the 112 2nd rejection over claim 54 is maintained for reasons mentioned in the previous office action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 36-38, 54-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for repairing a lesion or cavity in cartilaginous tissue comprising (1) preparing a solid implant comprising chondrocytes; (2) preparing an injectable cell-containing formulation comprising chondrocytes; (3) implanting the solid chondrocyte containing implant into a cavity or defect in cartilaginous tissue and (4) injecting the injectable chondrocyte-containing formulation into the interstices between the tissue and the solid implant, does not reasonably provide enablement for a method for replacing any tissue or body part or filling a void in any tissue comprising (1) preparing a solid implant comprising any cells; (2) preparing an injectable any cell-containing formulation; (3) implanting the solid implant into a cavity or defect in the tissue; and (4) injecting the injectable any cell-containing formulation into the interstices between the tissue and the solid implant. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

6. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor but rather is a conclusion reached by weighing many factors.

These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter., 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

7. 1) The nature of the invention. The invention involves a method for replacing any tissue or body part or filling a void in any tissue comprising (1) preparing any solid implant comprising any cells; (2) preparing an injectable cell-containing formulation comprising any cells; (3) implanting the solid implant into any cavity or defect in any tissue; and (4) injecting the injectable cell-containing formulation comprising any cells into the interstices between the tissue and the solid implant. The specification teaches "solid" as, "a non-porous material that retains its shape during handling" (page 5, lines 19-20). This "solid implant" thus reads on any material able to hold it's shape including whole organs for transplant purposes, such as liver, hearts, lungs, etc., as well as individual cells in culture media, as the individual cells are able to maintain their shape. The claims also read on implants from one tissue type being implanted in another tissue type. The claims also read on interspecies transplants (xenotransplants and xenographs).

8. 2) Number of working examples. Applicants have provided no working examples of the invention in human or animal models. All of applicant's examples are strictly drawn to chondrocyte implants. Applicants do show the ability to grow human chondrocytes on solid and injectable microcarriers (see examples 1-3). However, Examples 4 and 5 entitled "Implantation of Composite Cell-based Implants into Craniofacial Tissues" and "Implantation of Composite Cell-based Implant into Articular

Joints" are purely hypothetical and not reduced to practice. There is no teaching in the examples of using any other cell type other than chondrocytes in the implants. There is no teaching in the specification of how many cells are contained in the implants at time of implantation. The incubation times of culturing the cells in the examples varies up to 30 days in culture prior to implantation, but there is no teaching of how to know when one is to stop the in vitro culture an implant: it is based on cell density? On the solidification of the solid implant? If the cells are not chondrocytes, would the incubation times and densities be altered?

9. The examples of 1-3 teach the general use of solid implants comprising fibrinogen/thrombin, but not what specific type of fibrinogen or thrombin, nor in what quantities, etc. Example 3 further teaches the general use of other solid implants, stating, '[a]lternatively, other compositions may be used, such collagen, combinations of fibrin/collagen, transglutaminase-catalyzed binding systems, hyaluronic acid, calcium alginate gels, chitosan derivatives capable of gelling at body temperature, hydrogels such as polyacrylates, poly-vinyl alcohols, polyethylene glycols, or polyethyleneimines, or similar materials with suitable gelling compositions." However it provides no specific directions that would be necessary in order to reduce these materials to practice.

10. The examples do not provide how to adjust the solid or injectable implant compositions to account for the different tissues the implants are being placed in. Would the same solid implant for bone be placed in cartilage? Would the same solid implant for bone be placed in a liver or heart? A skilled artisan would have to perform undue experimentation in order to make and use the invention.

11. 3) Amount of direction or guidance present. The applicants provide general non-specific guidance on how to make solid implants comprising a variety of materials ranging from whole blood to polymers including polyethyleneimines (see page 8, lines 1-11). However, there is no specific teaching of how these solid implants are made (quantities, concentrations, incubation times, temperatures) without any cells other than a global statement comprising, "[i]n situ gelling of these materials may be initiated by thermal, enzymatic or chemical catalysis, pH or ionic strength changes or photo-initiation procedure" (page 8, lines 8-11).

12. Furthermore, applicants broadly teach that the implants comprise other cells than chondrocytes, such as, "osteoblasts, myoblasts, keratinocytes, fibroblasts such as those harvested from tendon, ligament, skin, meniscus or disk of the temporomandibular joint or intervertebral joint, or multi-potent stem cells that are capable of differentiating into matrix-producing cells, including mesenchymal stem cells, pluripotent stem cells from muscle, fat or skin, or embryonic stem cells" (page 9, lines 1-5). However, applicant does not teach how to modify the method in order to utilize these cell types. How are the cells isolated? How are they cultured? How are the multi-potent stem cells differentiated? There is no teaching on how to adjust culture conditions, how to isolate the cells, etc. Will all cells adhere to the microcarriers in the same manner? Will pluripotent stem cells differentiate into the correct cell type on whole blood solid implants? How would the multi-potent stem cells be able to differentiate into specific cell types in vivo?

13. Applicants provide no teaching on whether the cells are derived from the same patient (autologous implants) or different donors (heterologous implants). There is no teaching of how the skilled artisan would be able to implant heterologous cells from one donor to another. Are the donors all human? Are there inter-species implants? What species are included as donors? All mammals? All vertebrates? All eukaryotes? How would a skilled artisan choose what donor cells to use? A skilled artisan would have to perform undue experimentation in order to make and use the invention.

14. 2) State of the art. The method of implanting a cell containing solid implant with an injectable cell-containing implant reads on methods of gene therapy and organ transplantation comprising interspecies xenografts and stem cells.

15. Selden et al (Cellular Therapies for liver replacement. Transplant Immunology, 2004. 12:273-288) teaches a variety of xenograft methodologies for liver replacement, including whole organ replacement (both human to human as well as non-human to human) (see page 273), partial tissue grafts (page 275), injections of autologous and heterologous hepatocytes (page 276). Selden teaches that a major obstacle for whole organ transplants and xenografts is recipient immune response and rejection. He teaches that patients in need of liver transplants are often naturally immunosuppressed, and the additional immunosuppressive therapies required to treat the patient to prevent immune rejection of the implant often leads to sepsis and death in these patients (page 275-276). Selden points out that different liver diseases (cirrhosis vs. metabolic deficiencies from an inherited disease) require different therapies because of the function and nature of the disease state (page 275). Selden also points out that

engraftment of hepatocytes into alternate organs, such as the spleen, result in hepatocytes that are able to grow in a spleen, however it is not a therapeutic goal (page 274). Selden further teaches that the majority of liver cells are terminally differentiated and non-dividing, and that providing enough cells to repopulate a liver remains a challenge (page 280). He also states, that generally, proliferating cells are less differentiated, and therefore may not provide adequate liver specific functions (page 281).

16. Selden also teaches that interspecies organ transplants have no long term success rates (page 273), and that a major concern using inter-species cells for live therapies is the possibility of the cross-over of species-specific retrovirus infection in humans (page 281).

17. Selden also teaches that the additional therapies include the encapsulation of hepatocytes in matrices and scaffolds, including laminin, fibronectins and collagens, but that the different types of matrices and concentrations of matrices effect hepatocyte functions, and must be taken into account (page 282-283).

18. Thus Selden teaches that cell or organ implants between species, and between different tissue types, as well as those implants that are encapsulated are affected by the type and location of the implant, the species of the donor, the disease state of the tissue, and the type of implant itself, and that if not accounted for cause rejection of the graft and potential death to the patient.

19. De Bari et al (Failure of In Vitro-Differentiated Mesenchymal Stem Cells From the Synovial Membrane to Form Ectopic Stable Cartilage In Vivo. Arthritis & Rheumatism,

2004. 50(1):142-150) teaches that Mesenchymal Stem Cells that were cultured in vitro to differentiate into chondrocytes were unable to maintain their differentiation when implanted in vivo (see abstract). De Bari teaches that the cells were injected as individual cells or cell masses (solids) but both were unable to form ectopic stable cartilage in vivo (see pages 142-143, and 146). He teaches that the loss of the chondrocyte markers in vivo, even after the injection of the cell masses, "indicate[s] that preserving tissue integrity is not sufficient to maintain stable-cartilage phenotype in vivo after subcutaneous implantation" (page 146). Thus De Bari teaches cell mass implants of chondrocytes differentiated from mesenchymal stem cells were unable to maintain their phenotype in vivo.

20. Poliard et al (Lineage-Dependent Collagen Expression and Assembly during Osteogenic or Chondrogenic Differentiation of a Mesoblastic Cell Line. Experimental Cell Research, 1999. 253:385-395) teaches that the differentiation of progenitor cells is highly dependent upon the type and concentration of the extracellular matrix surrounding the cells (see abstract). In his study he focused on the expression of collagens type I, II, III, V, XI, VI, IX and X that had roles in differentiating the C1 cell line into osteoblasts, chondrocytes or adipose cells, and found that differentiation was in direct correlation to different collagen formation and culture conditions, but that the precise role of the extracellular matrix is still unknown in osteogenic differentiation and chondrogenic differentiation (page 391-392).

21. Xiao et al (Immunosuppression and Xenotransplantation of Cell for Cardiac Repair. The Society of Thoracic Surgeons, 2004. 77:737-744) teaches that

xenotransplantation and xenografts into hearts needs to address immunorejection of the transplants in order to develop and implement fully successful therapies and treatments (see abstract). He further teaches that xenotransplanted cardiomyocytes from fetal rat hearts into adult rat hearts are eventually rejected (page 740), and that transplanted stems cells do not always differentiate into cardiomyocytes in vivo after grafting (page 741). Xiao et al further points to concerns of the cross-over of pathogens such as porcine endogenous retrovirus that may be able to infect human recipients (page 741).

22. Yang et al (Application of Xenogeneic Stem Cells for Induction of Transplantation Tolerance: Present Stat and Future Directions. Springer Seminars Immunity, 2004. 26:187-200) teaches that there is a greater immune response between xenografts and xenotransplants between different species than of allografts. He further teaches that there is no current therapy available that has been effective in inducing long term tolerance between interspecies xenografts, and that there may be actual genetic incompatibility between the species that may ultimately be a large obstacle to over come before such transplants and grafts are successful long term (see abstract).

23. Taken together, the art recognized problems of cell transplants, whether in solid form or injectable, include many obstacles that have not been solved including interspecies incompatibility, loss of differentiation of stem cells in vivo, lack of the ability of stem cells to differentiate in vivo, potential health risks due to cross-over pathogens, and the undefined but important role of the extracellular matrix components and culture conditions of cells in the differentiation of pluripotent cells, all of which in combination are not addressed by applicant, nor are currently solved in the art. Thus a skilled

artisan would have to perform undue experimentation in order to make and use the invention.

24. 4) Unpredictability of the art. The art is highly unpredictable: the art recognized problems of cell transplants, whether in solid form or injectable, include many obstacles that have not been solved including interspecies incompatibility, loss of differentiation of stem cells in vivo, lack of the ability of stem cells to differentiate in vivo, potential health risks due to cross-over pathogens, and the undefined but important role of the extracellular matrix components and culture conditions of cells in the differentiation of pluripotent cells are currently not solved in the art. Thus a skilled artisan would have to perform undue experimentation in order to make and use the invention.

25. 5) Level of skill in the art. The level of skill is high: the art recognized problems of cell transplants, whether in solid form or injectable, include many obstacles that have not been solved including interspecies incompatibility, loss of differentiation of stem cells in vivo, lack of the ability of stem cells to differentiate in vivo, potential health risks due to cross-over pathogens, and the undefined but important role of the extracellular matrix components and culture conditions of cells in the differentiation of pluripotent cells are currently not solved in the art. Thus a skilled artisan would have to perform undue experimentation in order to make and use the invention.

26. 7) The breadth of the claims. The breadth of the claims are broad. The claims read on a method for replacing any tissue or body part or filling a void in any tissue comprising (1) preparing a any solid implant comprising any cells; (2) preparing an injectable cell-containing formulation comprising any cells; (3) implanting the solid

implant into any cavity or defect in any tissue; and (4) injecting the injectable cell-containing formulation comprising any cells into the interstices between the tissue and the solid implant. The specification teaches "solid" as, "a non-porous material that retains its shape during handling" (page 5, lines 19-20). This "solid implant" thus reads on any material able to hold its shape including whole organs for transplant purposes, such as liver, hearts, lungs, etc., as well as individual cells in culture media, as the individual cells are able to maintain their shape. The claims also read on implants from one tissue type being implanted in another tissue type. The claims also read on interspecies transplants.

27. Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, including the highly unpredictable art, the scarcity of working examples provided by applicant, the lack of guidance by the applicant, and the broad nature of the invention it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

28. It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st (enablement) and 35 USC 103(a). While these rejections may seem contradictory, they are not because each is based upon a different legal analysis, i.e. sufficiency of the disclosure of the instant application to support claims under 35 USC 112, 1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See *In re Hafner*, 161 USPQ 783 (CCPA 1969)).

Claim Rejections - 35 USC § 103

29. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

30. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

31. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

32. Claims 36-38, 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simon et al (US Patent No 6,632,246) and Griffith-Cima (US Patent 5,709,854) in view of Grande et al (US Patent 5,906,934). Claims 36-38, 54-57 recite a method for replacing a tissue or body part or filling a void in a tissue comprising (1) preparing a solid implant (2) preparing an injectable cell-containing formulation (3) implanting the solid implant into a cavity or defect in the tissue and (4) injecting the injectable cell-containing formulation into the interstices between the tissue and the solid implant. The solid implant and the injectable formulation comprise cells, particularly chondrocytes. The injectable formulation of cells, which creates the interface layer of cells, comprises cultured stem cells. Additionally, the method recites that the solid implant comprising a microcarrier is cultured with chondrocytes for a longer time period that the injectable cell containing implant comprising a microcarrier.

33. Simon et al (US Patent No 6,632,246) teaches a method for replacing cartilage in a body utilizing preformed molded solid plugs, which are used in conjunction with a fluid polymer. Simon states the object of the invention is "to provide artificial cartilage devices which are fabricated as plugs...which are used to fill a void in cartilage...such that the plugs are capable of being utilized either individually, or in a plurality as part of a mosaicplasty...It is another object of the present invention to provide artificial cartilage plugs for anchoring a flowable polymer to the bony base of a lesion site [and] to provide an orthopedic surgical procedure for removing a defective portion of cartilage and refilling the void cavity with one or more artificial, biocompatible, preformed cartilage replacement plugs" (Column 6, lines 27-54). Simon teaches that the plugs are formed

by "molding biostable polycarbonate polyurethane material into preformed shapes" (column 12, lines 11-13), and that these plugs are fabricated as "solid elements" (column 12, lines 44-45). Simon teaches the production of the solid implants using the microcarrier "biocompatible polyurethane polymer beads" (column 19, lines 36-38). Simone teaches four distinct methods for the production of the solid polymer implant from the production of flowable polymers (see methods 1-4, columns 17-20). Simon teaches that a flowable polymer is a "polymer that, when initially placed in to the application site or mold, at the time of use, has reactive components in the prepolymerized or early polymerization state and is physically fluid or flowable, but is capable of curing (polymerizing) to a solid state relatively quickly after application" (column 11, lines 58-61).

34. Simon further states "once the anchor plugs are in place, a flowable polymer is introduced into the defect site. The flowable polymer will flow into the lesion site, including into the defect site. The flowable polymer will flow into the lesion site, including into and around the implanted plug" (column 24, lines 10-14). Thus Simon teaches a method for replacing a tissue or body part for filling a void in a tissue comprising 1) preparing a solid implant using a microcarrier; 2) preparing an injectable formulation using a microcarrier; 3) implanting the solid implant into the cavity; and 4) injecting the flowable formulation between the solid implant and the surrounding tissue. Simon does not teach that the fluid implant comprises stem cells, nor that the culturing conditions for preparing of the solid-cell containing implant or the fluid injectable cell-containing implant.

35. Griffith-Cima (US Patent 5,709,854) teaches a method for the repair or replacement of cartilage tissue using biocompatilble and biodegradable solid or injectable polymer scaffolds that are cultured with chondrocytes. Griffith teaches that the liquid polymer is mixed with chondrocytes while still in a fluid state and then injected into a lesion site and allowed to harden in vivo, or the polymer is poured into a preformed mold and allowed to harden with the cells prior to implantation (see column 1 line 40 through column 2 line 24). Griffith-Cima teaches that the injection of the implants allows for a reconstruction procedure that is minimally invasive without extensive surgery (column 1, lines 14-20), and the design of solid implants allows for custom moldings of implants individual for the patient (column 2, lines 18-24). Since Griffith-Cima teaches that the cells are cultured with the polymer, and the injected fluid polymer hardens in the patient, while the solid implants harden outside the patient, inherently, the chondrocytes are incubated with the solid implant longer than the fluid implant. Griffith-Cima does not teach that the fluid implant comprises stem cells.

36. Grande et al (US Patent 5,906,934) teaches a method of cartilage repair using the implantation of stem cells in a solid or fluid polymer. He teaches that implanted stem cells will differentiate into cartilage if implanted into cartilage or bone if implanted into bone (see abstract, and column 3, lines 24-27). Grande teaches the stem cells are cultured with a hydrogel polymer that is in a fluid solution. The stem cell and hydrogel solution can be injected directly into the lesion site and allowed to hard in vivo, or can be injected into a mold that is mold that is made of the lesion site and allowed to harden prior to implantation (see columns 6-7). Grande teaches that one of the advantages of

using stem cells over chondrocytes, because stem cells give more flexibility in repair sites: chondrocytes are good for repairing cartilage, but not good for repairing lesion sites in cartilage areas that are adjacent to bone. Thus stem cells that are placed in the interface between cartilage and bone will regenerate both cell types in the appropriate areas (column 2, lines 24 through column 3, line 20).

37. A skilled artisan would have been motivated to combine the teaching of Simon on a method of repairing cartilage using solid implant plugs, wherein the solid implant is implanted, and an injectable polymer is injected between the plug and the interstitial space with the teaching of Griffith-Cima et al on solid or injectable fluid implant comprising polymer matrices further comprising chondrocytes for cartilage repair, wherein culturing the cells for the solid implant is longer than the fluid implant because the solid implant hardens outside of the body prior to implantation, but the fluid implant is injected directly into the lesion site, further with teaching of Grande on the use of solid or liquid polymer implant comprising stem cells for the regeneration of cartilage because the method of Simon allows for a very custom fit of the solid implant where any crevices not filled by the solid implant are filled by the polymer, and the use of polymer matrices comprising either chondrocytes or stem cells allows for the polymers (either hard or soft) to comprise cartilage cells, or cartilage precursor cells (stem cell), that will become cartilage in vivo and be able to differentiate into the proper cell type in interface areas between cartilage and bone. It would have been obvious to the skilled artisan to combine the teaching of Simon on a method of repair cartilage using solid implant plugs, wherein the solid implant is implants and an injectable polymer is injected

between the plug and the interstitial space with the teaching of Griffith-Cima et al on solid or injectable fluid polymer matrices comprising chondrocytes for cartilage repair, wherein culturing the cells for the solid implant is longer than the fluid implant because the solid implant hardens outside of the body prior to implantation, but the fluid implant is injected directly into the lesion site, further with teaching of Grande on the use of solid or liquid polymer implant comprising stem cells for the regeneration of cartilage because the use of chondrocyte or stem cells in solid or fluid polymers was well known in the art, and the method of Simon would have been improved by using the method of implanting a first solid implant followed by a second injectable implant, wherein both implants comprise cartilage forming cells would provide a more accurate fit of a lesion site for the implant, and an implant that would comprise the correct tissue type. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Conclusion

38. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kam/03/21/07

DAVID GUZO
PRIMARY EXAMINER